As the Examiner indicated at page 3 of the Official Action, Sanders et al. do not teach or suggest generation of an expression vector capable of expressing the GS gene or host cells transformed with said gene.

The Examiner's attention is respectfully directed to the fact that the invention as presently claimed is directed to a vector which is amplifiable in a transformed host cell. It is respectfully submitted that none of the Sanders et al., Alberts et al. or Watson et al. publications teach or suggest such a vector.

Applicants have previously argued that the Sanders et al. publication does not provide the motivation for one of ordinary skill in the art to clone the complete GS gene, to make vectors encoding GS or to express said gene in a transformed host cell. The Examiner, in response, alleges "several motivations" in the Sanders et al. publication. Applicants discuss each of these alleged "motivations" in turn.

(i) "the GS gene product 'is responsible for the conversion of glutamate and ammonia to glutamine, which has been described as the most versatile of all amino acids....'"

Applicants respectfully submit that the statement in Sanders et al. relied upon by the Examiner is merely describing the enzymatic function of glutamine synthetase, and nothing more. Such a mere statement of function cannot provide motivation to make either vectors comprising a DNA encoding a complete mammalian

glutamine synthetase, or transformed host cells containing such a vector.

Furthermore, while it is agreed that the GS gene product converts glutamate and ammonia to glutamine, and that glutamine may be a versatile amino acid, this does not provide a motivation to make the vectors and host cells presently claimed, due to the fact that there is no disclosure in Sanders et al. as to any benefit to be derived from such vectors and transformed host cells. It is respectfully submitted that only the present specification provides this teaching of the benefits of the vectors and host cells claimed.

(ii) ".... that GS levels '... may be regulated in vivo and in vitro as a result of cellular differentiation, glucocorticoid hormone levels and medium glutamine levels...' and thereby be important in understanding cellular differentiation, etc."

The Examiner's conclusion that GS levels may be "important in understanding cellular differentiation, etc." cannot be drawn from the Sanders et al. publication. It is respectfully submitted that there is no evidence of record that an amplifiable vector encoding a complete mammalian GS would be considered "important" to understanding such things as cellular differentiation. Nor is there evidence of record that transformed host cells comprising such a vector would be "important" to understanding cellular differentiation.

The Examiner must therefore be relying on his own personal knowledge in this regard and is respectfully requested to provide

declaratory evidence on this point pursuant to 37 CFR 1.107(b). Otherwise, Applicants respectfully submit that it should be agreed that the Sanders et al. publication does not teach or suggest that GS levels may be "important in understanding cellular differentiation."

(iii) "'Gene amplification has also been reported as an oncogenic phenomenon." It is noted that the Examiner provides no rebuttable rationale or conclusion as to why this statement in Sanders et al. provides any motivation to one of ordinary skill in the art as to the usefulness of the vectors and host cells presently claimed.

Indeed, even if true (which is not admitted), this statement in Sanders et al. does not teach or suggest any benefit of the vector or host cell specifically claimed. It again merely states a purported phenomenon that may or may not be associated with gene amplification in general, and does not reach the question of amplification of the glutamine synthetase gene in particular.

For the reasons given, Applicants again respectfully submit that the Sanders et al. publication simply could not provide the motivation or incentive to one of ordinary skill in the art at the time to make the presently claimed vectors and host cells. It is further respectfully submitted that, lacking such motivation or incentive, the person of ordinary skill in the art could not have found the invention obvious in view of the cited publications.

Reconsideration is respectfully requested.

In response to Applicants' previous argument on the paucity of evidence that Sanders et al. actually cloned a portion of the glutamine synthetase gene, the Examiner stated at page 5 of the Official Action that this argument is "contradictory to applicants' sworn statements in the instant specification."

Specifically, the Examiner relies on the statement at page 6 of the specification as follows:

> "Recently Sanders and Wilson (Sanders P.G. and Wilson R.H., The EMBO Journal, 3, 1, 65-71, 1984) have described the cloning of an 8.2 kb BglII fragment containing DNA coding for GS from the genome of an Msx resistant Chinese hamster ovary (CHO) cell line KGIMS." (emphasis added by the Examiner)

There is nothing of record, including Applicants' argument, to indicate that this statement in the specification is incorrect. Indeed, this is what Sanders et al. purport to describe. However, the specification does not go on to say that this alleged description of cloning the GS gene was in fact true. Indeed, the specification immediately thereafter states:

> "However this fragment does not appear to contain a complete GS gene and it was not sequenced."

Thus, the specification specifically states that the DNA cloned by Sanders et al. did not appear to contain a complete GS gene. It is respectfully submitted that the invention as presently claimed features a vector comprising a DNA encoding a complete mammalian glutamine synthetase and host cells transformed with such a vector. Additionally, Figure 2 of the present specification depicts the DNA

sequence of a complete mammalian glutamine synthetase. Yet further, the specification provides functional evidence that this DNA encodes a mammalian glutamine synthetase. It is respectfully submitted that Sanders et al. do not provide the proof of the cloning of a DNA encoding even a partial GS coding sequence. Thus, one of ordinary skill in the art could not be motivated by the disclosure of Sanders et al. to arrive at the claimed invention.

The Examiner indicated at page 6 of the Official Action that Applicants' arguments, if true, create what is "potentially a best mode rejection." Applicants respectfully submit that this cannot be the case. The best mode under 35 U.S.C. §112, first paragraph, is directed to the subjective nature of what the inventor believes at the time of filing is the best mode in which to practice the invention. It is respectfully submitted that there is nothing on the record to indicate that the best mode of practicing the invention is not contained in the specification as originally filed.

The Examiner also attempts to support his argument by referring to the disclosure in the specification as to the procedure used by Sanders et al. However, the inconclusive nature of the Sanders et al. disclosure is respectfully submitted to support Applicants' position. That Sanders et al. do not conclusively prove the cloning of even part of the GS gene does not mean that the disclosure in the specification is similarly defective. Indeed, the present specification goes much further than Sanders et al. to this end, giving both the DNA sequence and

functional data in support of the cloning of a DNA encoding a complete mammalian glutamine synthetase.

It is also respectfully submitted that the "best mode" requirement is related to the claimed invention, and the claimed invention is not a method of cloning a GS gene, which is all that the Sanders et al. publication purports to describe and to which Applicants arguments are directed.

With respect to the unobviousness of the invention given the demonstration of amplification of exogenous GS even in the presence of the endogenous gene, the Examiner states both that the claims do not currently recite this feature and that this argument appears to be more relevant to the allowed method claims in U.S. Patent No. 5,122,464. However, the property of amplification in the presence of an endogenous GS gene serves to make the vector and host cell claimed unobvious in much the same way as the patented method is unobvious.

That is, one of ordinary skill in the art could not know that the claimed vector would be amplifiable in a host cell regardless of the presence of an endogenous GS gene, without first consulting the present specification. It is respectfully submitted that there is nothing in the documents of record that would teach or suggest this feature of the claimed vector. It is therefore respectfully submitted that this property of the vector could not have been obvious to the ordinary artisan at the time.

With regard to the Alberts et al. and Watson et al. documents, these are in no way directed to the GS gene, but rather are general

in nature. It is respectfully submitted that these documents cannot, therefore, fill the deficiencies left by the Sanders et al. publication regarding the claimed vectors and host cells. It is further respectfully submitted that general teachings, such as those in Alberts et al. and Watson et al., cannot make obvious the specifically claimed invention.

Reconsideration of this rejection is respectfully requested.

Relying on 35 U.S.C. §103, the Examiner rejected claims 52 to 54 and 56 to 60 over Sanders et al. in view of Alberts et al. or Watson et al. all further in view of Axel et al. The Examiner cites Axel et al. for disclosing "the co-amplification of two different linked or un-linked DNAs," and alleges that the invention is "essentially an obvious variation" of the teachings of Axel et al.

Applicants respectfully submit that the invention as presently claimed is directed to amplifiable vectors and host cells comprising these vectors. There is nothing in Sanders et al. to teach or suggest to the ordinary artisan that such vectors would be amplifiable. Although the chromosomal locus of the GS gene may be amplified, the "minimum" amplification unit disclosed in Sanders et al. is 50,000 base pairs (Sanders et al., page 69, right column), which, it is submitted, would lead the person of ordinary skill to the conclusion that GS would not be suitable for use in a vector.

Thus, there would be no motivation for one of ordinary skill in the art to look to the disclosure of Axel et al. concerning the

co-amplification of genes. Furthermore, there is no mention in Axel et al. of use of a vector comprising a DNA encoding a complete mammalian glutamine synthetase as a amplifiable unit. The only mention of such a vector is in the present specification. Therefore, absent viewing the disclosure of the specification, one of ordinary skill could not know the claimed vector would be amplifiable, and thus would not turn to the disclosure of Axel et al.

It is respectfully submitted that since the disclosure of an amplifiable vector is not given in the cited documents, the Examiner must be using hindsight in fashioning this rejection. The case law is clear that such hindsight is impermissible in fashioning a rejection.

The Examiner again alleges that "arguments with regard to amplification of the GS gene and a foreign gene sequence in cells containing a normal endogenous GS gene do not appear to pertain to the instant claims." While it is agreed that this advantage underscores the unobvious of the allowed method claims, there is also nothing in the documents cited that teaches or suggests this advantage of the claimed vectors. That is, without the disclosure in the present specification, one of ordinary skill in the art could not know that there could even exist an amplifiable vector comprising a DNA encoding a complete mammalian glutamine synthetase, and that such a vector would be amplifiable regardless of the presence of an endogenous GS gene.

The Examiner further recites disclosure from column 8 of the Axel et al. patent as supporting his position. The Examiner does not, however, indicate the relevance, if any, of the recited passage.

For the sake of completeness, Applicants point out the passage in Axel et al. referred to by the Examiner is related to the use of a mutant DHFR gene. See column 6, lines 62 to 66. The cited paragraph is therefore considered to be irrelevant to the invention as presently claimed, which features a DNA encoding a complete mammalian glutamine synthetase, and not a mutant DHFR gene.

Reconsideration is respectfully requested in view of the above. Applicants, furthermore, intend to submit Declaratory evidence supporting unexpected results as to the improvement related to the use of GS amplification compared with that using the DHFR system (since the Axel et al. patent is directed, in part, to amplification using DHFR/methotrexate) which will further establish the non-obviousness of the present invention.

Relying on 35 U.S.C. §112, first paragraph, the Examiner alleges that the specification fails to provide an adequate written description of the invention and, on this basis, rejects claims 53 and 54. It is noted that despite the Examiner's reference to the "written description" requirement of 35 U.S.C. §112, first paragraph, his argument appears to be directed to the "enablement" requirement. The Examiner maintains that the one skilled in the art needs to "exactly duplicate" the claimed plasmids. However,

Applicants respectfully submit that these claims are directed to the plasmids disclosed in the specification and any obvious variant thereof. Thus, one need not necessarily "exactly" duplicate the claimed plasmids in order to practice the invention.

Applicants further respectfully submit that in a circumstance such as the present, M.P.E.P. §2411 requires as follows:

> "This ground of rejection should be accompanied by evidence of [sic: or] scientific reasoning to support the conclusion that a person skilled in the art could not make or use the invention defined in and commensurate with the claims without access to the specific biological deposit."

It is respectfully submitted that the Examiner has failed to provide such evidence or reasoning and has, therefore, not met his burden. Rather, it is respectfully submitted that the Examiner has merely made an unsupported conclusion. It is further respectfully submitted that without such evidence or valid scientific reasoning, the specification must be taken as enabling.

Relying on 35 U.S.C. §112, first paragraph, the Examiner rejected claims 39, 40, 44 to 47, 50 to 52, 55, 56, 58, 60 and 61, alleging that the disclosure is enabling only for claims directed to a hamster GS gene and vectors containing said gene. Applicants respectfully submit that, following the description of the invention in the specification, there is no reason the skilled artisan could not make or use the claimed vectors and host cells employing any mammalian GS gene.

The Examiner has provided no evidence or sound scientific reasoning as to why one skilled in the art could not use the specification as a guide for the cloning of any mammalian GS gene, and subsequent use of that DNA in the claimed vectors and transformed host cells.

It is respectfully submitted that the Examiner has the burden of supplying such evidence or reasoning in the record. However, the Examiner gives no evidence as to why he feels that any mammalian species would not have a GS gene and why such a gene could not be isolated given the procedures described in the application. Furthermore, as GS is necessary for the normal production of glutamine, one skilled in the art would expect all mammalian species to have a DNA encoding this activity. Thus, the Examiner has again only set forth a conclusion, without also supplying the substantive basis upon which that conclusion rests.

Relying on 35 U.S.C. §112, first paragraph, the Examiner rejected claims 57 and 59, alleging that the disclosure is enabling only for claims directed to "CHO-K1 myeloma cells." It is first noted that CHO-K1 cells are not myeloma cells, but rather are derived from Chinese hamster ovary tissue.

It is respectfully submitted that the Examiner has again not supported his conclusion as to the non-enablement of the invention. There is no reason to believe that the vector of the present invention could not be used in cell lines apart from CHO-K1 and myeloma cells. As the Examiner has pointed out, it is known that

the GS enzyme is an important enzyme for all cell types, as it is used in the production of an essential amino acid, glutamine. The skilled person, given the teaching in the present application, would have expected that the vectors of the present invention are useful in all cell types. Certainly, given the teaching in the present application, the skilled person would have been able to transform any cell line with the vector, in the expectation of being able to amplify.

Thus, because the GS gene is not restricted to the specifically claimed cells but is essential for the production of glutamine in all cells, the skilled artisan would expect to be able to use this gene in virtually all cell types.

Moreover, it is respectfully submitted that nothing in our Patent Laws requires the specification to specifically exemplify each and every embodiment of the invention. Rather, the specification needs only supply the skilled artisan with the tools for making and using the invention by means of routine experimentation. It is respectfully submitted that the present specification clearly is adequate in this regard.

Relying on 35 U.S.C. §112, first paragraph, the Examiner rejected claim 44. As claim 44 is not currently pending, this rejection is moot.

For the reasons given, Applicants respectfully submit that the rejections should be withdrawn and that their application is in

condition for allowance. Applicants request notice of such allowability in the next communication from the Examiner.

The Examiner is invited to call the undersigned attorney should any minor matter remain.

Respectfully submitted,

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